

PCT

WELTORGANISATION FÜR GEISTIGES EIGENTUM
Internationales Büro



F6

INTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE
INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

(51) Internationale Patentklassifikation 6 : C07D		A2	(11) Internationale Veröffentlichungsnummer: WO 98/16507
		(43) Internationales Veröffentlichungsdatum:	23. April 1998 (23.04.98)
(21) Internationales Aktenzeichen: PCT/EP97/05432 (22) Internationales Anmeldedatum: 2. Oktober 1997 (02.10.97) (30) Prioritätsdaten: 196 42 319.8 14. Oktober 1996 (14.10.96) DE 196 42 320.1 14. Oktober 1996 (14.10.96) DE 196 42 322.8 14. Oktober 1996 (14.10.96) DE 196 42 323.6 14. Oktober 1996 (14.10.96) DE (71) Anmelder (für alle Bestimmungsstaaten ausser US): BAYER AKTIENGESELLSCHAFT [DE/DE]; D-51368 Leverkusen (DE). (72) Erfinder; und (75) Erfinder/Anmelder (nur für US): STRAUB, Alexander [DE/DE]; Moospfad 30, D-42113 Wuppertal (DE). ROBYR, Chantal [CH/DE]; Bismarckstrasse 23, D-45470 Mülheim (DE). NIEWÖHNER, Ulrich [DE/DE]; Garten- strasse 3, D-42929 Wermelskirchen (DE). JAETSCH, Thomas [DE/DE]; Eintrachtstrasse 105, D-50668 Köln (DE). FEURER, Achim [DE/DE]; Schlinghofener Strasse 36, D-51519 Odenthal (DE). KAST, Raimund [DE/DE]; Badische Strasse 7, D-42389 Wuppertal (DE). STASCH, Johannes-Peter [DE/DE]; Alfred-Nobel-Strasse 109, D-42651 Solingen (DE). PERZBORN, Elisabeth [DE/DE];		Am Tescher Busch 13, D-42327 Wuppertal (DE). HÜTTER, Joachim [DE/DE]; Teschensudberger Strasse 13, D-42349 Wuppertal (DE). DEMBOWSKY, Klaus [DE/DE]; Bismarckstrasse 85, D-42115 Wuppertal (DE). ARLT, Dieter [DE/DE]; Papenhauser Strasse 10, D-32657 Lemgo (DE). (74) Gemeinsamer Vertreter: BAYER AKTIENGE- SELLSCHAFT; D-51368 Leverkusen (DE). (81) Bestimmungsstaaten: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO Patent (GH, KE, LS, MW, SD, SZ, UG, ZW), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI Patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Veröffentlicht Ohne internationalen Recherchenbericht und erneut zu veröffentlichen nach Erhalt des Berichts.	
(54) Title: NEW HETEROCYCLYLMETHYL-SUBSTITUTED PYRAZOL DERIVATES			
(54) Bezeichnung: NEUE HETEROCYCLYLMETHYL-SUBSTITUIERTE PYRAZOLDERIVATE			
(57) Abstract			
Disclosed are new heterocyclylmethyl-substituted pyrazol derivatives, the preparation thereof and their use as drug products, particularly for treating cardiovascular diseases.			
(57) Zusammenfassung			
Die vorliegende Erfindung betrifft neue Heterocyclylmethyl-substituierte Pyrazolderivate, Verfahren zu ihrer Herstellung und ihre Verwendung als Arzneimittel, insbesondere als Arzneimittel zur Behandlung von Herz-Kreislauf-Erkrankungen.			

Le 17 32080 US patents 6166027
 SNs 644,305
 645,834
 648,082



US006166027A

United States Patent [19]**Straub et al.**[11] **Patent Number:** **6,166,027**[45] **Date of Patent:** **Dec. 26, 2000**[54] **HETEROCYCLYMETHYL-SUBSTITUTED
PYRAZOLE DERIVATIVES AND THEIR USE
FOR TREATING CARDIOVASCULAR
DISEASES**[75] **Inventors:** **Alexander Straub**, Wuppertal; **Chantal Fürstner**, Mülheim/Ruhr; **Ulrich Niewöhner**, Wermelskirchen; **Thomas Jaetsch**, Köln; **Achim Feurer**, Odenthal; **Raimund Kast**, Wuppertal; **Johannes-Peter Stasch**, Solingen; **Elisabeth Perzborn**; **Joachim Hütter**, both of Wuppertal; **Klaus Dembowski**, Schriesheim; **Dieter Arlt**, Lemgo, all of Germany[73] **Assignee:** **Bayer Aktiengesellschaft**, Leverkusen, Germany[21] **Appl. No.:** **09/284,172**[22] **PCT Filed:** **Oct. 2, 1997**[86] **PCT No.:** **PCT/EP97/05432**§ 371 Date: **Apr. 9, 1999**§ 102(e) Date: **Apr. 9, 1999**[87] **PCT Pub. No.:** **WO98/16507****PCT Pub. Date:** **Apr. 23, 1998**[30] **Foreign Application Priority Data**

Oct. 14, 1996	[DE]	Germany	196 42 319
Oct. 14, 1996	[DE]	Germany	196 42 320
Oct. 14, 1996	[DE]	Germany	196 42 322
Oct. 14, 1996	[DE]	Germany	196 42 323

[51] **Int. Cl.⁷** **A61K 31/506; A61P 9/00**[52] **U.S. Cl.** **514/269; 544/238; 544/295;
544/328; 544/333; 544/405**[58] **Field of Search** 546/275.7; 544/333;
514/269[56] **References Cited****FOREIGN PATENT DOCUMENTS**

135 781	4/1985	European Pat. Off. .
220573	5/1987	European Pat. Off. .
667 345	8/1995	European Pat. Off. .
25 03 815	8/1975	Germany .
96 20192	7/1996	WIPO .

OTHER PUBLICATIONS

Chemical Abstracts, vol. 125, No. 3, Jul. 15, 1996, Abstract No. 3363m, S. Guo, et al., "Preparation . . . inhibitors" & CN 1 112 926 (Yongxin Pharmaceutical Industry Co., Ltd. Peop. Rep. China) Dec. 6, 1995.

S.-M. Yu et al., "Inhibition of Platelet . . . Vivo", vol. 87, No. 9, May 1, 1996, pp. 3758-3767.

C.-C. Wu, et al. "YC-1 inhibited . . . cyclase", British Journal of Pharmacology, vol. 116, No.13, 1995, pp. 1973-1978.

C.R. Self, et al., "Romazarit: A Potential Disease . . . Drug" Journal of Medicinal Chemistry, vol. 34, No. 2, 1991, Washington, U.S. pp. 772-777.

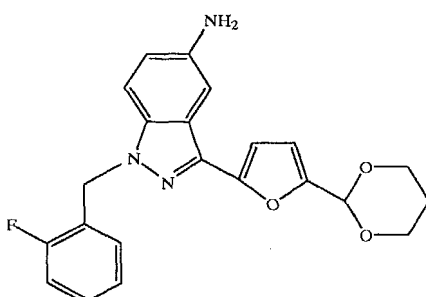
G. Capozzi, et al., "Neighbouring Group . . . 3-benzamiodopropyne", Tetrahedron Letters, vol. 22, No. 34, 1981 pp. 3325-3328.

Primary Examiner—Robert W. Ramsuer*Attorney, Agent, or Firm*—Norris, McLaughlin & Marcus, P.A.[57] **ABSTRACT**

The present invention relates to new heterocyclylmethyl-substituted pyrazole derivatives, processes for their preparation and their use as medicaments, in particular as medicaments for treatment of cardiovascular diseases.

14 Claims, No Drawings

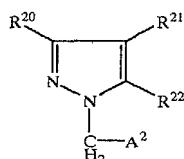
TABLE IV/5-continued

Ex. No.	Structure	Yield/ melting point	R _f
IV/203		45% 158° C.	0.14 (H:EE 1:1)

*EE = ethyl acetate
H = hexane
P = petroleum ether
T = toluene

What is claimed is:

1. A 1-Heterocyclyl-methyl-substituted pyrazole of the formula (II-I)



in which

R²⁰ represents a 6-membered aromatic heterocyclic ring having up to 3 nitrogen atoms, which is optionally substituted up to 3 times in an identical or different manner by formyl, carboxyl, hydroxyl, mercaptyl, straight-chain or branched acyl, alkoxy, alkylthio or alkoxycarbonyl having in each case up to 6 carbon atoms, nitro, cyano, azido, halogen, phenyl and/or by a group of the formula



wherein

R²³ and R²⁴ are identical or different and denote hydrogen or straight-chain or branched acyl having up to 6 carbon atoms or straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by cycloalkyl having 3 to 6 carbon atoms, hydroxyl, amino or by straight-chain or branched alkoxy, acyl or alkoxycarbonyl having in each case up to 5 carbon atoms,

or

R²³ and R²⁴, together with the nitrogen atom, form a 3- to 7-membered saturated or partly unsaturated heterocyclic ring, which can optionally additionally contain an oxygen or sulphur atom or a radical of the formula —NR²⁵,

wherein

R²⁵ denotes hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,

and/or is substituted by straight-chain or branched alkyl having up to 6 carbon atoms, which in its turn can be substituted by hydroxyl, amino, halo carboxyl, straight-chain or branched acyl, alkoxy, alkoxycarbonyl or acylamino having in each case up to 5 carbon atoms or by a radical of the formula —OR²⁶,

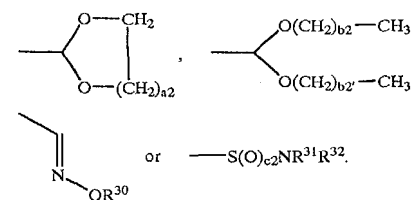
wherein

R²⁶ denotes straight-chain or branched acyl having up to 5 carbon atoms or a group of the formula —SiR²⁷R²⁸R²⁹,

wherein

R²⁷, R²⁸ and R²⁹ are identical or different and denote aryl having 6 to 10 carbon atoms or alkyl having up to 6 carbon atoms,

and/or is optionally substituted by a radical of the formula



wherein

b2 and b2' are identical or different and denote the number 0, 1, 2 or 3,

a2 denotes the number 1, 2 or 3,

R³⁰ denotes hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,

c2 denotes the number 1 or 2 and

R³¹ and R³² are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 10 carbon atoms, which is optionally substituted by cycloalkyl having 3 to 8 carbon atoms or by aryl having 6 to 10 carbon atoms, which in its turn can be substituted by halogen, or

denote aryl having 6 to 10 carbon atoms, which is optionally substituted by halogen, or

denote cycloalkyl having 3 to 7 carbon atoms, or

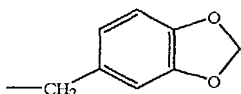
R³¹ and R³², together with the nitrogen atom, form a 5- to 7-membered saturated heterocyclic ring, which

161

can optionally contain a further oxygen atom or a radical —NR^{33} ,

wherein

R^{33} denotes hydrogen, straight-chain or branched alkyl having up to 4 carbon atoms or a radical of the formula



or denotes benzyl or phenyl, wherein the ring systems are optionally substituted by halogen,

R^{21} and R^{22} , including the double bond, form a 5-membered aromatic heterocyclic ring having a heteroatom from the series consisting of S, N and/or O, or a phenyl ring, which are optionally substituted up to 3 times in an identical or different manner by formyl, mercaptyl, carboxyl, hydroxyl, amino, straight-chain or branched acyl, alkylthio, alkoxy or alkoxycarbonyl having in each case up to 6 carbon atoms, nitro, cyano, azido, halogen, phenyl or straight-chain or branched alkyl having up to 6 carbon atoms, which in its turn can be substituted by hydroxyl, amino, carboxyl, straight-chain or branched acyl, alkoxy or alkoxycarbonyl having in each case up to 5 carbon atoms, or are optionally substituted by a group of the formula $\text{—S(O)}_{c2}\text{—NR}^{31}\text{R}^{32}$ wherein c_2 , R^{31} and R^{32} have the abovementioned meaning of c_2 , R^- and R^{32} and are identical to or different from these,

A^2 represents phenyl or a 5- to 6-membered aromatic or saturated heterocyclic ring having up to 3 heteroatoms from the series consisting of S, N and/or O, which is optionally substituted up to 3 times in an identical or different manner by mercaptyl, hydroxyl, formyl, carboxyl, straight-chain or branched acyl, alkylthio, alkoxyacyl, alkoxy or alkoxycarbonyl having in each case up to 6 carbon atoms, nitro, cyano, trifluoromethyl, azido, halogen, phenyl or straight-chain or branched alkyl having up to 6 carbon atoms, which in its turn can be substituted by hydroxyl, carboxyl, straight-chain or branched acyl, alkoxy or alkoxycarbonyl having in each case up to 5 carbon atoms,

and/or is substituted by a group of the formula $\text{—(CO)}_{d2}\text{—NR}^{34}\text{R}^{35}$,

wherein

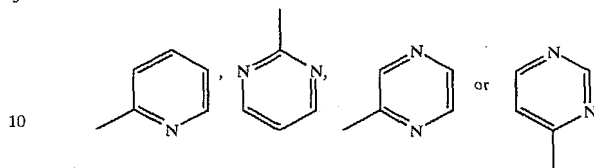
d_2 denotes the number 0 or 1,

R^{34} and R^{35} are identical or different and denote hydrogen, phenyl, benzyl or straight-chain or branched alkyl or acyl having in each case up to 5 carbon atoms, and an isomer, salt and N-oxide thereof.

162

2. A compound according to claim 1 of the formula (II-I), in which

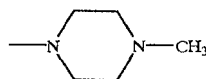
R^{20} represents a radical of the formula



which are optionally substituted up to 3 times in an identical or different manner by formyl, carboxyl, hydroxyl, straight-chain or branched acyl, alkoxy or alkoxycarbonyl having in each case up to 5 carbon atoms, nitro, cyano, azido, fluorine, chlorine, bromine, phenyl and/or by a group of the formula $\text{—NR}^{23}\text{R}^{24}$,

wherein

R^{23} and R^{24} are identical or different and denote hydrogen or straight-chain or branched acyl having up to 4 carbon atoms or straight-chain or branched alkyl having up to 4 carbon atoms, which is optionally substituted by hydroxyl, amino or by straight-chain or branched alkoxy having up to 3 carbon atoms, or R^{23} and R^{24} , together with the nitrogen atom, form a morpholine ring or a radical of the formula

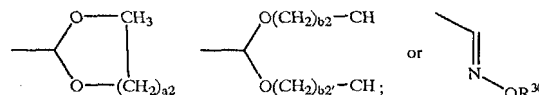


and/or are substituted by straight-chain or branched alkyl having up to 5 carbon atoms, which in its turn can be substituted by hydroxyl, amino, fluo carboxyl, straight-chain or branched acyl, alkoxy, alkoxycarbonyl or acylamino having in each case up to 4 carbon atoms or by a radical of the formula —OR^{26} ,

wherein

R^{26} denotes straight-chain or branched acyl having up to 4 carbon atoms,

and/or are optionally substituted by a radical of the formula



wherein

b_2 and b_2' are identical or different and denote the number 0, 1, 2 or 3,

a_2 denotes the number 1, 2 or 3,

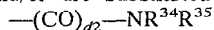
R^{30} denotes hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,

R^{21} and R^{22} , including the double bond, form a furyl, thienyl or phenyl ring, which are optionally substituted up to 3 times in an identical or different manner by formyl, carboxyl, hydroxyl, amino, straight-chain or branched acyl, alkoxy or alkoxycarbonyl having in

each case up to 5 carbon atoms, nitro, cyano, azido, fluorine, chlorine, bromine, phenyl or straight-chain or branched alkyl having up to 5 carbon atoms, which in its turn can be substituted by hydroxyl, amino, carboxyl, straight-chain or branched acyl, alkoxy or alkoxy carbonyl having in each case up to 4 carbon atoms,

A² represents phenyl, or represents tetrahydropyranyl, furyl, tetrahydrofuranlyl, morpholinyl, pyrimidyl, pyridazinyl or pyridyl, which are optionally substituted up to twice in an identical or different manner by hydroxyl, formyl, carboxyl, straight-chain or branched acyl, alkylthio, alkyloxyacyl, alkoxy or alkoxy carbonyl having in each case up to 4 carbon atoms, fluorine, chlorine, bromine, nitro, cyano, trifluoromethyl or straight-chain or branched alkyl having up to 4 carbon atoms, which in its turn can be substituted by hydroxyl, carboxyl, straight-chain or branched acyl, alkoxy or alkoxy carbonyl having in each case up to 4 carbon atoms,

and/or are substituted by a group of the formula



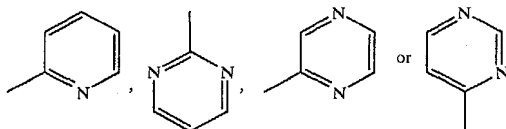
wherein

d₂ denotes the number 0 or 1,

R³⁴ and R³⁵ are identical or different and denote hydrogen, phenyl, benzyl or straight-chain or branched alkyl or acyl having in each case up to 4 carbon atoms, and an isomer, salt and N-oxide thereof.

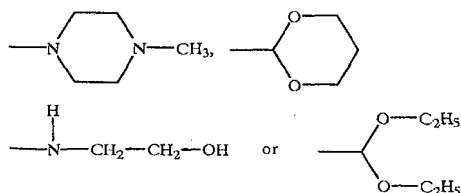
3. A compound according to claim 1 of the formula (II-I), in which

R²⁰ represents a radical of the formula



wherein the ring systems are optionally substituted up to 3 times in an identical or different manner by formyl, straight-chain or branched acyl, alkoxy or alkoxy carbonyl having in each case up to 4 carbon atoms, methylamino, amino, fluorine, chlorine, bromine, cyano, azido or straight-chain or branched alkyl having up to 4 carbon atoms, which in its turn can be substituted by hydroxyl, carboxyl, amino, straight-chain or branched acyl, alkoxy, alkoxy carbonyl or acylamino having in each case up to 3 carbon atoms,

and/or are optionally substituted by a radical of the formula

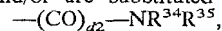


R²¹ and R²², including the double bond, form a furyl, thienyl or phenyl ring, which are optionally substituted up to twice in an identical or different manner by formyl, carboxyl, hydroxyl, amino, straight-chain or branched acyl, alkoxy or alkoxy carbonyl having in

each case up to 4 carbon atoms, nitro, cyano, fluorine, chlorine, phenyl or straight-chain or branched alkyl having up to 3 carbon atoms, which in its turn can be substituted by hydroxyl, amino, carboxyl, straight-chain or branched acyl, alkoxy or alkoxy carbonyl having in each case up to 3 carbon atoms,

A² represents phenyl, tetrahydropyranyl, tetrahydrofuranlyl, furyl or pyridyl, which are optionally substituted up to twice in an identical or different manner by formyl, carboxyl, straight-chain or branched acyl, alkylthio, alkyloxyacyl, alkoxy or alkoxy carbonyl having in each case up to 3 carbon atoms, fluorine, chlorine, bromine, nitro, cyano, trifluoromethyl or represents straight-chain or branched alkyl having up to 3 carbon atoms, which in its turn can be substituted by hydroxyl, carboxyl, straight-chain or branched acyl, alkoxy or alkoxy carbonyl having in each case up to 3 carbon atoms,

and/or are substituted by a group of the formula



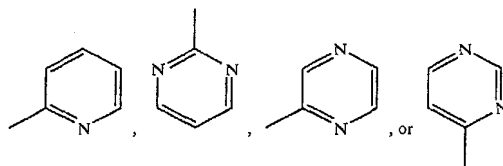
wherein

d₂ denotes the number 0 or 1,

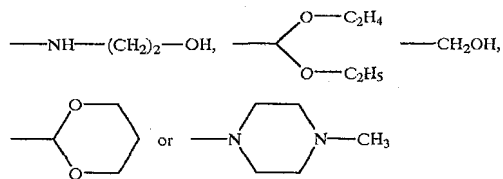
R³⁴ and R³⁵ are identical or different and denote hydrogen or straight-chain or branched alkyl or acyl having in each case up to 3 carbon atoms, and an isomer, salt and N-oxide thereof.

4. A compound according to claim 1 of the formula (II-I), in which

R²⁰ represents a radical of the formula



wherein the abovementioned heterocyclic ring systems are optionally substituted up to 3 times in an identical or different manner by methyl, fluorine, formyl, amino, cyano, methoxy, methoxycarbonyl, methylamino, chlorine or by a radical of the formula



R²¹ and R²², including the double bond, together form a phenyl ring and

A² represents phenyl, which is optionally substituted by fluorine or cyano, and an isomer, salt and N-oxide thereof.

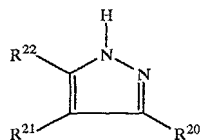
5. A pharmaceutical composition comprising at least one compound of the formula (II-I) according to claim 1.

6. A pharmaceutical composition comprising at least one compound of the formula (II-I) according to claim 1 and at least one organic nitrate or an NO donor.

7. A pharmaceutical composition comprising at least one compound of the general formula (II-I) according to claim 1 and compounds which inhibit the breakdown of cyclic guanosine monophosphate (cGMP).

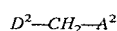
8. A process for preparing a compound of the formula (II-I) according to claim 1, comprising:

A) reacting compounds of the formula (II-II)



in which

R^{20} , R^{21} and R^{22} are defined as in claim 1, with compounds of the formula (II-III)



in which

A^2 is defined as in claim 1,

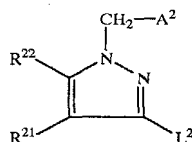
and

D^2 represents triflate or halogen,

in an inert solvent and, optionally in the presence of a base,

or

B) reacting compounds of the formula (II-IV)



in which

A^2 , R^{21} and R^{22} are defined as in claim 1

and

L^2 represents a radical of the formula $-\text{SnR}^{36}\text{R}^{37}\text{R}^{28}$, ZnR^{39} , iodine or triflate

wherein

R^{36} , R^{37} and R^{38} independently denote straight-chain or branched alkyl having up to 4 carbon atoms

and

R^{39} denotes hydrogen with compounds of the formula (II-V)



(II-II) 5

10

15

20

(II-IV) 30

35

40

45

50

(II-V)

in which

R^{20} is defined as in claim 1

and

in the case where $L^2 = \text{SnR}^{36}\text{R}^{37}\text{R}^{38}$ or ZnR^{39}

T^2 represents triflate or halogen,

and

in the case where $L^2 = \text{iodine}$ or triflate,

T^2 represents a radical of the formula $\text{S}^{36}\text{R}^{37}\text{R}^{38}$, ZnR^{39} or $\text{BR}^{40}\text{R}^{41}$,

wherein

R^{36} , R^{37} , R^{38} and R^{39} have the above mentioned meanings

and

R^{40} and R^{41} independently denote hydroxyl aryloxy having 6 to 10 carbon atoms or straight-chain or branched alkyl or alkoxy having in each case up to 5 carbon atoms, or together form a 5- or 6-membered carbocyclic ring,

in a palladium-catalysed reaction in an inert solvent.

9. The process according to claim 8, which is for the preparation of a compound of formula (II-I) which contains a radical $-\text{S}(\text{O})_{c2}.\text{NR}^{31}\text{R}^{32}$ or $-\text{S}(\text{O})_{cd}.\text{NR}^{31}\text{R}^{32}$, said process further comprising reacting an unsubstituted compound of formula (II-I) with thionyl chloride to produce an intermediate product, and thereafter reacting said intermediate product with $\text{HNR}^{31}\text{R}^{32}$ or $\text{HNR}^{31}\text{R}^{32}$.

10. The process according to claim 8, which further comprises introducing or varying R^{20} , R^{21} , R^{22} and/or A^2 by customary methods, preferably by reduction, oxidation, splitting off of protective groups and/or nucleophilic substitution.

11. The process according to claim 8 wherein, D^2 represents bromine or T^2 represents bromine.

12. Method for the treatment of cardiovascular diseases, said method comprising administering to a patient in need thereof an effective amount thereof of at least one compound of the formula (II-I) according to claim 1.

13. Method for preventing or treating the consequences of a cerebral infarction event said method comprising administering to a patient in need thereof an effective amount thereof of at least one compound of the formula (II-I) according to claim 1.

14. The method according to claim 13, wherein the cerebral infarction event is an apoplexia cerebri selected from the group consisting of apoplexy, cerebral ischaemias and crania-cerebral trauma.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,166,027
DATED : December 26, 2000
INVENTOR(S) : Straub et al.

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 166.

Line 10, delete "BR⁴⁰R", and substitute -- BR⁴⁰R⁴¹, --

Line 28, delete "HNR³¹R³²," and substitute -- HNR³¹R³², --

Signed and Sealed this

Twenty-sixth Day of February, 2002

Attest:

A handwritten signature in black ink, appearing to read "James E. Rogan", with a horizontal line drawn underneath it.

Attesting Officer

JAMES E. ROGAN
Director of the United States Patent and Trademark Office



US006387940B1

(12) **United States Patent**
Straub et al.

(10) **Patent No.:** **US 6,387,940 B1**
(45) **Date of Patent:** **May 14, 2002**

(54) **HETEROCYCLYLMETHYL-SUBSTITUTED
PYRAZOLE DERIVATIVES**

(58) **Field of Search** 548/361.1, 235;
514/403

(75) **Inventors:** Alexander Straub, Wuppertal; Chantal
Fürstner, Mülheim/Ruhr; Ulrich
Niewöhner, Wermelskirchen; Thomas
Jaetsch, Köln; Achim Feurer,
Odenthal; Raimund Kast, Wuppertal;
Johannes-Peter Stasch, Solingen;
Elisabeth Perzborn; Joachim Hütter,
both of Wuppertal; Klaus Dembowski,
Schriesheim; Dieter Arlt, Lemgo, all of
(DE)

(56) **References Cited**

FOREIGN PATENT DOCUMENTS

DE	25 03 815	8/1975
EP	135 781	4/1985
EP	220573	5/1987
EP	667 345	8/1995
WO	96 20192	7/1996

OTHER PUBLICATIONS

Chemical Abstracts, vol. 125, No. 3, Jul. 15, 1996, Abstract
No. 33633m, S. Guo, et al., "Preparation . . . inhibitors" &
CN 1 112 926 (Yongxin Pharmaceutical Industry Co., Ltd.
Peop. Rep. China) Dec. 6, 1995.

S.-M. Yu et al., "Inhibition of Platelet . . . Vivo", vol. 87, No.
9, May 1, 1996, pp. 3758-3767.

C.-C. Wu, et al. "YC-1 inhibited . . . cyclase", British
Journal of Pharmacology, vol. 116, No. 13, 1995, pp.
1973-1978.

C.R. Self, et al., "Romazarit: A Potential Disease . . . Drug"
Journal of Medicinal Chemistry, vol. 34, No. 2, 1991,
Washington, U.S. pp. 772-777.

G. Capozzi, et al., "Neighbouring Group . . . 3-benzami-
dopropyne", Tetrahedron Letters, vol. 22, No. 34, 1981 pp.
3325-3328.

Primary Examiner—Robert W. Ramsuer

(74) *Attorney, Agent, or Firm*—Norris McLaughlin &
Marcus

(57) **ABSTRACT**

The present invention relates to new heterocyclylmethyl-
substituted pyrazole derivatives, processes for their prepa-
ration and their use as medicaments, in particular as medi-
caments for treatment of cardiovascular diseases.

15 Claims, No Drawings

(73) **Assignee:** Bayer Aktiengesellschaft, Leverkusen
(DE)

(*) **Notice:** Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 8 days.

(21) **Appl. No.:** 09/644,179

(22) **Filed:** Aug. 23, 2000

Related U.S. Application Data

(62) Division of application No. 09/284,172, filed as application
No. PCT/EP97/05432 on Oct. 2, 1997, now Pat. No. 6,166,
027.

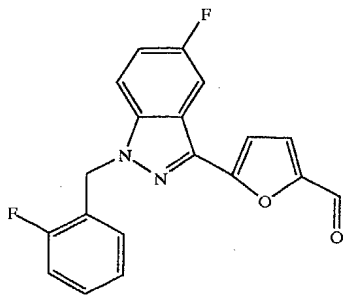
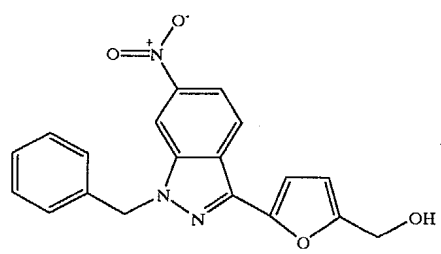
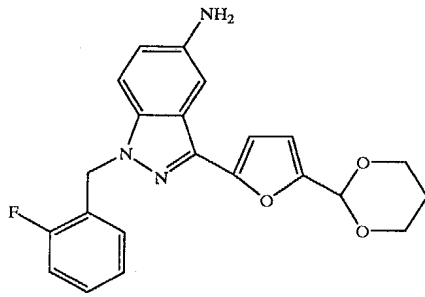
(30) **Foreign Application Priority Data**

Oct. 14, 1996	(DE)	196 42 320
Oct. 14, 1996	(DE)	196 42 323
Oct. 14, 1996	(DE)	196 42 322
Oct. 14, 1996	(DE)	196 42 319

(51) **Int. Cl.⁷** A61K 31/4155; A61P 9/12;
C07D 407/04

(52) **U.S. Cl.** 514/403; 546/275.7; 548/235;
548/236; 548/181; 548/311.7; 548/361.1

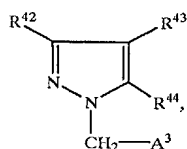
TABLE IV/5-continued

Ex. No.	Structure	Yield/ melting point R_f
IV/201		89% 0.61 131° C. (H:EE 1:1)
IV/202		76% 0.39 152° C. (H:EE 1:1)
IV/203		45% 0.14 158° C. (H:EE 1:1)

*EE = ethyl acetate
H = hexane
P = petroleum ether
T = toluene

What is claimed is:

1. A 3-Heterocyclyl-substituted pyrazole derivative of the formula (III-I)



in which

R^{42} represents a saturated 6-membered heterocyclic ring having up to 2 heteroatoms from the series consisting of S, N and/or O or represents a 5-membered aromatic or saturated heterocyclic ring having 2 to 3 heteroatoms from the series consisting of S, N and/or O, which can also be bonded via a nitrogen atom and which are

50

(III-I)

55

60

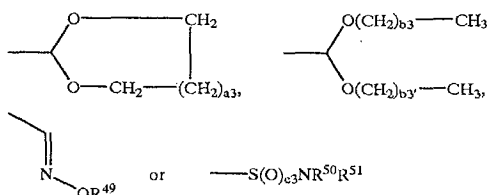
optionally substituted up to 3 times in an identical or different manner by formyl, phenyl, mercaptyl, carboxyl, trifluoromethyl, hydroxyl, straight-chain or branched acyl, alkoxy, alkylthio or alkoxycarbonyl having in each case up to 6 carbon atoms, nitro, cyano, halogen, phenyl or straight-chain or branched alkyl having up to 6 carbon atoms, which in its turn can be substituted by hydroxyl, halogen, trifluoromethyl, amino, carboxyl, straight-chain or branched acyl, alkoxy, alkoxycarbonyl or acylamino having in each case up to 5 carbon atoms or by a radical of the formula $-OR^{45}$, wherein

R^{45} denotes straight-chain or branched acyl having up to 5 carbon atoms or a group of the formula $-SiR^{46}R^{47}R^{48}$, wherein

R^{46} , R^{47} and R^{48} are identical or different and denote aryl having 6 to 10 carbon atoms or alkyl having up to 6 carbon atoms,

163

and/or can be substituted by a radical of the formula



wherein

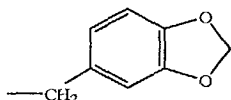
a3, b3 and b3' denote the number 0, 1, 2 or 3,

R⁴⁹ denotes hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,

c3 denotes the number 1 or 2 and

R⁵⁰ and R⁵¹ are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 10 carbon atoms, which is optionally substituted by cycloalkyl having 3 to 8 carbon atoms or by aryl having 6 to 10 carbon atoms, which in its turn can be substituted by halogen, or denote aryl having 6 to 10 carbon atoms, which is optionally substituted by halogen, or denote cycloalkyl having 3 to 7 carbon atoms, or R⁵⁰ and R⁵¹, together with the nitrogen atom, form a 5- to 7-membered saturated heterocyclic ring, which can optionally contain a further oxygen atom or a radical -NR⁵², wherein

R⁵² denotes hydrogen, straight-chain or branched alkyl having up to 4 carbon atoms or a radical of the formula



or denotes benzyl or phenyl, wherein the ring systems are optionally substituted by halogen,

R⁴³ and R⁴⁴, including the double bond, form a 5-membered aromatic heterocyclic ring having one heteroatom from the series consisting of N, S and/or O, or a phenyl ring, which are optionally substituted up to 3 times in an identical or different manner by formyl, carboxyl, hydroxyl, amino, straight-chain or branched acyl, alkoxy or alkoxycarbonyl having in each case up to 6 carbon atoms, nitro, cyano, halogen, phenyl or straight-chain or branched alkyl having up to 6 carbon atoms, which in its turn can be substituted by hydroxyl, amino, carboxyl, straight-chain or branched acyl, alkoxy or alkoxycarbonyl having in each case up to 5 carbon atoms,

and/or are optionally substituted by a group of the formula -S(O)c3NR⁵⁰R⁵¹, wherein c3, R⁵⁰ and R⁵¹ have the abovementioned meaning of c3, R⁵⁰ and R⁵¹ and are identical to or different from these,

A³ represents a 5- to 6-membered aromatic or saturated heterocyclic ring having up to 3 heteroatoms from the series consisting of S, N and/or O or phenyl, which are optionally substituted up to 3 times in an identical or different manner by amino, mercaptyl, hydroxyl, formyl, carboxyl, straight-chain or branched acyl, alkylthio, alkyloxyacyl, alkoxy or alkoxycarbonyl having in each case up to 6 carbon atoms, nitro, cyano,

164

trifluoromethyl, azido, halogen, phenyl or straight-chain or branched alkyl having up to 6 carbon atoms, which in its turn can be substituted by hydroxyl, carboxyl, straight-chain or branched acyl, alkoxy or alkoxycarbonyl having in each case up to 5 carbon atoms,

and/or is substituted by a group of the formula (-CO)_{d3}-NR⁵³R⁵⁴, wherein

d3 denotes the number 0 or 1,

R⁵³ and R⁵⁴ are identical or different and denote hydrogen, phenyl, benzyl or straight-chain or branched alkyl or acyl having in each case up to 5 carbon atoms,

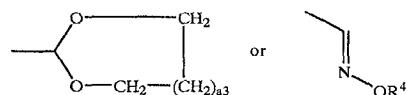
or an isomer or salt thereof.

2. A compound according to claim 1 of formula (III-I), in which

R⁴² represents pyranyl or morpholinyl, which are optionally substituted up to twice in an identical or different manner by formyl, trifluoromethyl, phenyl, carboxyl, hydroxyl, straight-chain or branched acyl, alkoxy or alkoxycarbonyl having in each case up to 5 carbon atoms, nitro, cyano, azido, fluorine, chlorine, bromine, phenyl or straight-chain or branched alkyl having up to 5 carbon atoms, which in its turn can be substituted by hydroxyl, halogen, trifluoromethyl, amino, carboxyl, straight-chain or branched acyl, alkoxy, alkoxycarbonyl or acylamino having in each case up to 4 carbon atoms, or by a radical of the formula -OR⁴⁵, wherein R⁴⁵ denotes straight-chain or branched acyl having up to 4 carbon atoms or a group of the formula -SiR⁴⁶R⁴⁷R⁴⁸, wherein

R⁴⁶, R⁴⁷ and R⁴⁸ are identical or different and denote straight-chain or branched alkyl having up to 4 carbon atoms,

and/or are substituted by a radical of the formula



wherein

a3 denotes the number 0, 1, 2 or 3,

R⁴⁹ denotes hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms,

R⁴³ and R⁴⁴, including the double bond, form a furyl, thienyl or phenyl ring, which are optionally substituted up to 3 times in an identical or different manner by formyl, carboxyl, hydroxyl, amino, straight-chain or branched acyl, alkoxy or alkoxycarbonyl having in each case up to 5 carbon atoms, nitro, cyano, azido, fluorine, chlorine, bromine, phenyl or straight-chain or branched alkyl having up to 5 carbon atoms, which in its turn can be substituted by hydroxyl, amino, carboxyl, straight-chain or branched acyl, alkoxy or alkoxycarbonyl having in each case up to 4 carbon atoms,

A³ represents tetrahydropyranyl, tetrahydrofuranlyl, thienyl, pyrimidyl, phenyl, morpholinyl, pyrimidyl, pyridazinyl or pyridyl, which are optionally substituted up to twice in an identical or different manner by hydroxyl, formyl, carboxyl, straight-chain or branched acyl, alkylthio, alkyloxyacyl, alkoxy or alkoxycarbonyl having in each case up to 4 carbon atoms, fluorine, chlorine, bromine, nitro, cyano, trifluoromethyl or straight-chain or branched alkyl having up to 4 carbon

165

atoms, which in its turn can be substituted by hydroxyl, carboxyl, straight-chain or branched acyl, alkoxy or alkoxy carbonyl having, in each case up to 4 carbon atoms,

and/or are substituted by a group of the formula $-(CO)_{d3}-NR^{53}R^{54}$, wherein

$d3$ denotes the number 0 or 1,

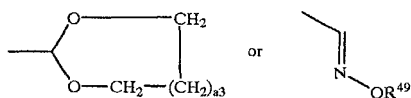
R^{53} and R^{54} are identical or different and denote hydrogen, phenyl, benzyl or straight-chain or branched alkyl or acyl having in each case up to 4 carbon atoms,

or an isomer or salt thereof.

3. A compound according to claim 1 of the formula (III-I), in which

R^{42} represents imidazolyl, oxazolyl, oxadiazolyl or thiazolyl, which are optionally substituted up to twice in an identical or different manner by formyl, trifluoromethyl, phenyl, straight-chain or branched acyl, alkoxy or alkoxy carbonyl having in each case up to 4 carbon atoms or straight-chain or branched alkyl having up to 4 carbon atoms, which in its turn can be substituted by hydroxyl, fluorine, chlorine, trifluoromethyl, carboxyl, amino, straight-chain or branched acyl, alkoxy, alkoxy carbonyl or acylamino having in each case up to 3 carbon atoms or by the radical of the formula $-O-CO-CH_3$,

and/or are substituted by a radical of the formula



wherein

$a3$ denotes the number 0, 1 or 2,

R^{49} denotes hydrogen or methyl,

R^{43} and R^{44} , including the double bond, form a furyl, thienyl or phenyl ring, which are optionally substituted up to twice in an identical or different manner by formyl, carboxyl, hydroxyl, amino, straight-chain or branched acyl, alkoxy or alkoxy carbonyl having in each case up to 4 carbon atoms, nitro, cyano, fluorine, chlorine, phenyl or straight-chain or branched alkyl having up to 3 carbon atoms, which in its turn can be substituted by hydroxyl, amino, carboxyl, straight-chain or branched acyl, alkoxy or alkoxy carbonyl having in each case up to 3 carbon atoms,

A^3 represents tetrahydropyranyl, phenyl, thienyl, pyrimidyl or pyridyl, which are optionally substituted up to twice in an identical or different manner by formyl, carboxyl, straight-chain or branched acyl, alkylthio, alkoxy acyl, alkoxy or alkoxy carbonyl having in each case up to 3 carbon atoms, fluorine, chlorine, bromine, nitro, cyano, trifluoromethyl, or straight-chain or branched alkyl having up to 3 carbon atoms, which in its turn can be substituted by hydroxyl, carboxyl, straight-chain or branched acyl, alkoxy or alkoxy carbonyl having in each case up to 3 carbon atoms,

and/or are substituted by a group of the formula $-(CO)_{d3}-NR^{53}R^{54}$, wherein

$d3$ denotes the number 0 or 1,

R^{53} and R^{54} are identical or different and denote hydrogen or straight-chain or branched alkyl or acyl having in each case up to 3 carbon atoms, or an isomer or salt thereof.

166

4. A compound according to claim 1 of the formula (III-I) in which

R^{42} represents imidazolyl, oxazolyl, thiazolyl or oxadiazolyl, which are optionally substituted up to twice in an identical or different manner by ethoxycarbonyl, phenyl or by methyl or ethyl, wherein the alkyl radicals in their turn can be substituted by hydroxyl, chlorine, ethoxycarbonyl, oxycarbonylmethyl or methoxy,

R^{43} and R^{44} together, including the double bond, represent phenyl, which is optionally substituted by nitro, A^3 represents phenyl or phenyl which is substituted by fluorine, or pyrimidyl

or an isomer or salt thereof.

5. A pharmaceutical composition comprising at least one compound of the formula (III-I) according to claim 1.

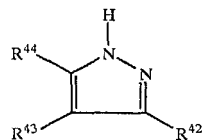
6. A pharmaceutical composition comprising a combination of at least one compound of the formula (III-I) according to claim 1 and at least one organic nitrate or an NO donor.

7. A pharmaceutical composition comprising a combination of at least one compound of the formula (III-I) according to claim 1 and compounds which inhibit the breakdown of cyclic guanosine monophosphate (cGMP).

8. Process for the preparation of a compound according to claim 1 of the formula (III-I), comprising

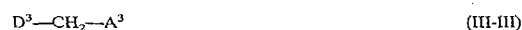
[A3] reacting a compound of the formula (III-I)

(III-II)



in which

R^{42} , R^{43} and R^{44} have the meaning in claim 1, with a compound of the formula (III-III)



in which

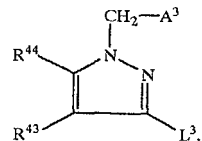
A^3 has the meaning in claim 1, and

D^3 represents triflate or halogen,

in an inert solvent, optionally in the presence of a base, or

[B3] reacting a compound of the formula (III-IV)

(III-IV)



in which

A^3 , R^{43} and R^{44} have the abovementioned meaning and L^3 represents a radical of the formula $-SnR^{55}R^{56}R^{57}ZnR^{58}$, iodine, bromine or triflate, wherein

R^{55} , R^{56} and R^{57} are identical or different and denote straight-chain or branched alkyl having up to 4 carbon atoms and

167

R^{58} denotes halogen,
with a compound of the formula (III-IV)



(III-V),

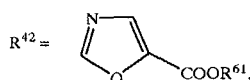
in which

R^{42} has the abovementioned meaning and
in the case where $L^3 = \text{Sn}R^{55}R^{56}R^{57}$ or $\text{Zn}R^{58}$,
 T^3 represents triflate or represents halogen, and
in the case where L^3 -iodine, bromine or triflate,
 T^3 represents a radical of the formula $\text{Sn}R^{55}R^{56}R^{57}$,
 $\text{Zn}R^{58}$ or $\text{BR}^{59}R^{60}$, wherein

R^{55} , R^{56} , R^{57} and R^{58} have the abovementioned
meaning of R^{55} , R^{56} , R^{57} and R^{58} and are identical
to or different from these, and

R^{59} and R^{60} are identical or different and denote
hydroxyl, aryloxy having 6 to 10 carbon atoms or
straight-chain or branched alkyl or alkoxy having
in each case up to 5 carbon atoms, or together
form a 5- or 6-membered carbocyclic ring,

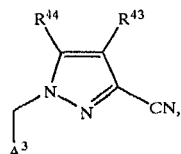
in a palladium-catalysed reaction in an inert solvent, or
[C3] in the case where



in which

R^{61} represents straight-chain or branched alkyl having
up to 4 carbon atoms,

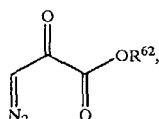
reacting a compound of the formula (III-VI)



(III-VI)

in which

A^3 , R^{43} and R^{44} have the abovementioned meaning,
with a diazo compound of the formula (III-VII)



(III-VII)

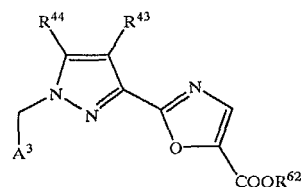
in which

R^{62} represents straight-chain or branched alkyl having
up to 4 carbon atoms,

in the presence of a copper salt or rhodium salt to give a
compound of the formula (III-1a)

168

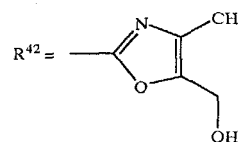
(III-1a)



in which

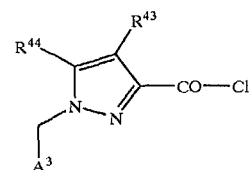
A^3 , R^{43} , R^{44} and R^{62} have the abovementioned
meaning, or

[D3] in the case where $R^{42} =$



reacting a compound of the formula (III-VIII)

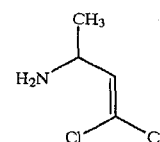
(III-VIII)



in which

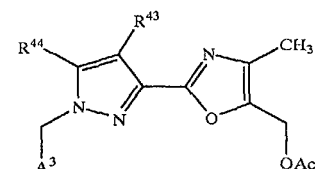
A^3 , R^{43} and R^{44} have the abovementioned meaning,
with the compound of the formula (III-IX)

(III-IX)



in the system $\text{NaOCO-CH}_3/\text{N-methylpyrrolidine}$
to give the compound of the formula (III-1b)

(III-1b)

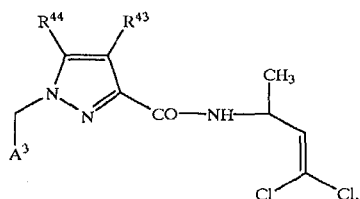


in which

R^{43} , R^{44} and A^3 have the abovementioned meaning,
and the acetyl group is then split off by the action of
potassium hydroxide in methanol, or

169

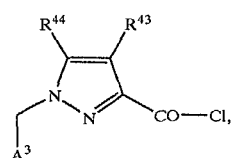
by reacting the compound of the formula (III-VIII) with the compound of the formula (III-IX), to give a compound of the formula (III-X)



in which

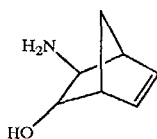
R^{43} , R^{44} and A^3 have the abovementioned meaning, and preparing the hydroxymethyl compound in a further step by reacting with potassium hydroxide, and optionally converting said hydroxy methyl compound into the corresponding alkoxy compound by alkylating said hydroxymethyl compound, or

[E3] reacting a compound of the formula (III-XI)

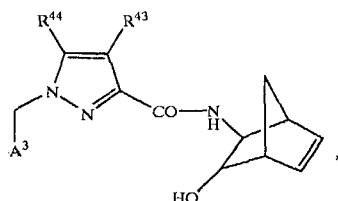


in which

A^3 , R^{43} and R^{44} have the abovementioned meaning, with the compound of the formula (III-XII)



to give the compound of the formula (III-XIII)

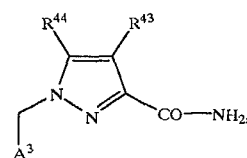


in which

A^3 , R^{43} and R^{44} have the abovementioned meaning, and then reacting said compound of formula (III-XIII) in a retro-Diels-Alder reaction, or

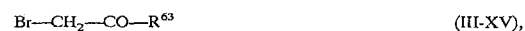
170

[F3] reacting a compound of the formula (III-XIV)



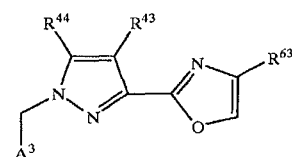
in which

A^3 , R^{43} and R^{44} have the abovementioned meaning, with a compound of the formula (III-XV),



in which

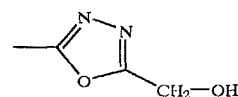
R^{63} denotes straight-chain or branched alkyl or alkoxy-carbonyl having in each case up to 4 carbon atoms, in an inert solvent to give the compound of the formula (III-Ic)



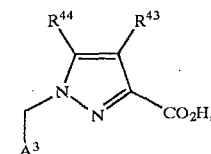
in which

A^3 , R^{43} , R^{44} and R^{63} have abovementioned meaning and, in the case of the esters ($R^{63}=CO_2-(C_1-C_4\text{-alkyl})$), reducing the compound of responding hydroxymethyl compound, or

[G3] in the case where $R^{43}=$



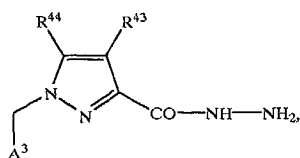
reacting a carboxylic acid of the formula (III-XVI)



in which

A^3 , R^{43} and R^{44} have the abovementioned meaning, with hydrazine hydrate to give the compound of the formula (III-XVII)

171

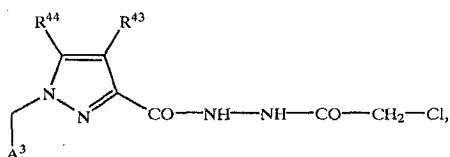


in which
A³, R⁴³ and R⁴⁴ have the abovementioned meaning,

and reacting said compound of the formula (III-XVII) 15
with the compound of the formula (III-XVIII)

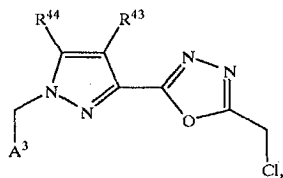


to give the compound of the formula (III-XIX)



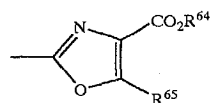
in which
A³, R⁴³ and R⁴⁴ have the abovementioned meaning, 35

and then, cyclizing the compound of the formula (III-XIX) by reacting with phosphorus oxytrichloride to give the compounds of the formula (III-Id)



in which
A³, R⁴³ and R⁴⁴ have the abovementioned meaning, or

[H3] in the case where R⁴² represents a radical of the 55
formula

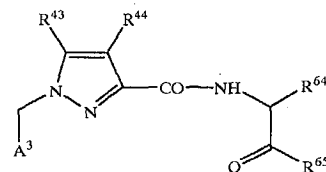


wherein
R⁶⁴ denotes hydrogen or straight-chain or branched 60
alkyl having up to 4 carbon atoms and

172

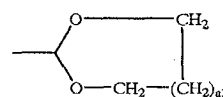
R⁶⁵ has the scope of meaning of the secondary sub-
stituents listed above under the heterocyclic radical
R⁴²,

5 reacting a compound of the formula (III-XX)



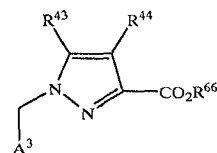
in which
A³, R⁴³, R⁴⁴, R⁶⁴ and R⁶⁵ have the abovementioned
meaning,
20 with PPh₃/I₂ optionally in the presence of a base, or

[13] in the case where R⁴² represents the group of the
formula



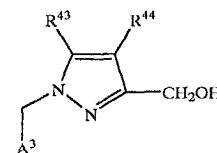
wherein a₃ denotes the number 0, 1, 2, or 3,

reducing a compound of the formula (III-XXI)



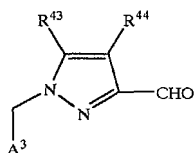
in which
A³, R⁴³ and R⁴⁴ have the abovementioned meaning and
R⁶⁶ has the abovementioned meaning of R⁶⁴ and is
identical to or different from this,

50 by customary methods to give a compound of the formula
(III-XXII)



in which
A³, R⁴³ and R⁴⁴ have the abovementioned meaning,
and then oxidizing the compound of the formula (III-
XXII) to give the compound of the formula (III-XXIII)

173

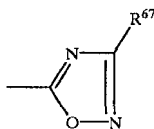


in which
A³, R⁴³ and R⁴⁴ have the abovementioned meaning, or

by directly converting the compound of the formula (III-XXI) by reduction into the compound of the formula (III-XXIII),

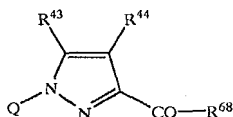
and, finally reacting the compound of the formula (III-XXIII) with 1,2- or 1,3-dihydroxy by conventional methods, or

[J3] in the case where R⁴² represents the radical of the formula



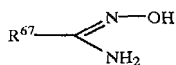
wherein
R⁶⁷ has the abovementioned meaning of R⁶⁵ and is identical to or different from this,

reacting a compound of the formula (III-XXIV)



in which
R⁴³ and R⁴⁴ have the abovementioned meaning and Q represents hydrogen or represents the -CH₂-A³ radical and
R⁶⁸ represents halogen or straight-chain or branched alkoxy having up to 4 carbon atoms, preferably chlorine, methoxy or ethoxy,

with a compound of the formula (III-XXV)



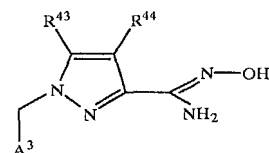
in which

174

R⁶⁷ has the abovementioned meaning,

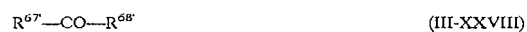
optionally in the presence of a base, and, in the case where Q=H, the product is then reacted with, a compound of the general formula A³-CH₂-Br (III-XXVI), in which A has the abovementioned meaning, or

reacting a compound of the formula (III-XXVII)



in which
A³, R⁴³ and R⁴⁴ have the abovementioned meaning

with a compound of the formula (III-XXVIII)



in which
R⁶⁷ has the abovementioned meaning of R⁶⁷ and is identical to or different from this and
R⁶⁸ has the abovementioned meaning of R⁶⁸ and is identical to or different from this optionally in the presence of a base.

9. The process according to claim 8, which is for the preparation of a compound of formula (III-I) which contains a radical -S(O)₂NR⁵⁰R⁵¹ or -S(O)₂NR⁵⁰R⁵¹, said process further comprising reacting an unsubstituted compound of formula (III-I) with thionyl chloride to produce an intermediate product, and thereafter reacting said intermediate product with HNR³¹R³² or HNR³¹R³².

10. The process according to claim 8, which further comprises introducing or varying R⁴², R⁴³ R⁴⁴ and/or A³ by reduction, oxidation, splitting off of protective groups and/or nucleophilic substitution.

11. The process according to claim 8, wherein, in [H3] D³ represents bromine or wherein in [B3] T³ represents bromine.

12. The process according to claim 8, wherein [H3] said base is triethylamine.

13. Method for the treatment of cardiovascular diseases, said method comprising administering to a patient in need thereof an effective amount thereof of at least one compound of the formula (III-I) according to claim 1.

14. Method for preventing or treating the consequences of a cerebral infarction event said method comprising administering to a patient in need thereof an effective amount thereof of at least one compound of the formula (III-I) according to claim 1.

15. The method according to claim 13, wherein the cerebral infarction event is an apoplexia cerebri selected from the group consisting of apoplexy, cerebral ischaemias and crania-cerebral trauma.

* * * * *